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INFLUENZA: Pigs, People and Public Health

Summary: Swine influenza viruses were first isolated in the United States in 1930. Since that time, they have become an economically important cause of respiratory disease in pigs throughout the world, and a human public health risk. The clinical signs/symptoms of influenza in pigs and people are remarkably similar, with fever, lethargy, lack of appetite and coughing prominent in both species. Furthermore, influenza viruses can be directly transmitted from pigs to people as "zoonotic" disease agents, and vice versa, from people to pigs. These interspecies infections are most likely to occur when people are in close proximity to pigs, such as in swine production barns, livestock exhibits at fairs, and slaughterhouses. Finally, because of their unique susceptibility to infection with influenza viruses of both mammalian and avian species, pigs can serve as intermediaries in the transmission of influenza viruses from birds to people. The birds of greatest concern are wild waterfowl, because these species provide an immense natural reservoir of influenza viruses. Replication of avian influenza viruses in pigs may allow them to adapt to and be able to efficiently infect mammals, and ultimately be transmitted to people. In addition, pigs can serve as hosts in which two (or more) influenza viruses can undergo "genetic reassortment." This is a process in which influenza viruses exchange genes during replication. The influenza viruses responsible for the worldwide 1957 and 1968 "pandemics" of human influenza were reassortant viruses with genes from both human and avian influenza viruses. Veterinarians can help pig producers design farms and develop management and personnel policies to minimize interspecies transmission of influenza viruses, thereby contributing to the health of both the swine and human populations.

Background: Influenza viruses exist in three "types," designated A, B and C. Of these, only influenza A viruses are significant concerns for the health of pigs. However, there are a large number of different "subtypes" of influenza A viruses. These subtypes are defined by the hemagglutinin (H or HA) and neuraminidase (N or NA) proteins of the virus. The HA is also the protein against which the host directs antibodies that can neutralize the virus. Of practical significance, there is no cross-protective immunity mediated by antibodies from one HA subtype to another.

There are 15 different subtypes of hemagglutinin and 9 different subtypes of neuraminidase among influenza A viruses. Subtypes are distinguished by differences in their genetic sequences, which translate into differences in their antigenic structure. The combination of HA and NA subtypes present in a virus are depicted by H and N designations, such as H1N1, H3N2, and so on. In the course of history, relatively few hemagglutinin and neuraminidase combinations have consistently circulated among pigs or people (predominantly H1N1, H1N2 and H3N2 in pigs, and H1N1, H1N2, H2N2 and H3N2 in people). In contrast, virtually all of the possible influenza A virus subtypes exist among wild waterfowl. In these birds, influenza viruses infect the gastrointestinal tract rather than the respiratory tract, which is the target organ in pigs, people, horses and other mammalian hosts of influenza viruses. The infections generally do not make the birds sick. In waterfowl, the viruses are shed in the bird's feces, and ultimately into the water of lakes and ponds that the birds visit during migrations, but also potentially onto the ground of barnyards and farm fields.

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Influenza viruses carry their genes on 8 separate pieces ("segments") of nucleic acid (RNA), rather than on one long single molecule. This structural feature has very important implications for virus evolution, because if two (or more) influenza viruses simultaneously infect cells in the same individual, then during replication, these viruses can exchange RNA segments with one another, thereby creating viruses with entirely new combinations of genes. This process of reassortment was the basis for the appearance of the pandemic viruses of 1957 (the "Asian" flu) and 1968 (the "Hong Kong" flu) in the human population. These pandemic viruses were responsible for millions of cases of human illness and tens of thousands of human deaths. In both cases, influenza viruses from waterfowl reassorted with the previously circulating human influenza viruses to create viruses with different hemagglutinin subtypes (from H1 to H2 in 1957 and from H2 to H3 in 1968). It is the change to a hemagglutinin subtype against which the population has no immunity ("antigenic shift") that causes these periodic global disease outbreaks of human disease.

How does this process of reassortment occur? In general, there is a functional barrier to infection of people with avian influenza viruses, and vice versa (the H5N1 infections of people in Hong Kong and China in 1997 and 2003 and the H7N7 infections of poultry workers and veterinarians in The Netherlands in 2003 being exceptions). This barrier is based, in part, on the fact that avian influenza viruses preferentially use receptors expressed on bird cells, and human viruses preferentially use receptors expressed in the human respiratory tract. Pigs, however, express both avian- and human-type receptors and can be infected with avian, human and swine influenza viruses. As such, they can serve as hosts in which avian viruses adapt to replication in mammals. For example, in 1979, an avian H1N1 virus of waterfowl-origin entered the pig population of northern Europe and soon became the dominant cause of influenza among European pigs. Subsequently, these avian H1N1 viruses were also isolated from people in Europe. Additionally, pigs are hypothesized to serve as the "mixing vessels" in which reassortment between avian and human influenza viruses can take place. The focus of such reassortment has historically been in Southeast Asia, the proposed "influenza epicenter," because agricultural practices in this region brought pigs, people and ducks into close contact with one another. However, it is now clear that influenza virus reassortment in pigs can occur anywhere in the world, as evidenced by reassortant viruses isolated from pigs in Europe and, most recently, in the United States. The later include human/swine/avian virus reassortant H3N2 viruses that have spread widely within the American pig population since their emergence in 1998, as well as "second generation" reassortant H1N2 and H1N1 viruses derived by genetic mixing between the reassortant H3N2 and classical swine H1N1 viruses. The H1N2 viruses have also been isolated subsequently from wild waterfowl and domestic turkeys. The isolation of these viruses from wild ducks was somewhat unexpected, but interspecies transmission of influenza viruses from pigs to domestic turkeys has been recognized previously on numerous occasions. In fact, turkey producers sometimes vaccinate their birds against swine virus infections. In contrast, transmission of influenza viruses between pigs and domestic chickens and other fowl, and vice versa, is very rarely reported.

Reducing interspecies transmission of influenza viruses: It is in the best interest of both human public health and animal health that transmission of influenza viruses from pigs to people, from people to pigs, from birds to pigs and from pigs to birds be minimized.

Interspecies transmission among pigs and people: About two dozen examples of zoonotic transmission of swine influenza viruses from pigs to people have been documented in the medical literature. Many more cases are likely to occur among swine workers. However, these will generally go unrecognized as anything but typical human influenza because the seasonal patterns of human and swine influenza largely overlap. A recent study by the author and colleagues from the Centers for Disease Control and Prevention sought to better understand the risks of zoonotic swine flu infections in the United States. In studying swine farmers, employees and their family members compared to an urban population from Milwaukee, Wisconsin, the factors most strongly associated with seropositivity to swine viruses were being a swine farm owner and/or a member of a farm owner's family, living on a swine farm, or entering a swine barn at least 4 days per week. (See suggested reading: C.W. Olsen, et al., Serologic evidence of H1 swine influenza virus infection in swine farm residents and employees, Emerg. Infect. Dis. 8 (2002) 814-819). Conversely, the impact of transmission of influenza viruses from people to pigs should not be under-estimated. The reassortant H3N2, H1N2 and H1N1 viruses currently circulating widely and causing disease throughout the swine population of the United States all contain human influenza virus genes.

The following steps are potentially useful to reduce transmission of influenza viruses between pigs and people:

- **Influenza virus vaccination of pigs** - While the swine influenza virus vaccines used today may not induce sterilizing immunity nor completely eliminate clinical signs of infection, vaccination of pigs can reduce the levels of virus shed by infected animals, and thus reduce the potential for human exposure and zoonotic infections.

- **Influenza virus vaccination of swine farm workers** - The vaccines produced on a yearly basis for the human population contain only human, not swine, strains of influenza viruses. Nonetheless, these vaccines are likely to provide some level of protection against infection with swine viruses of the same hemagglutinin subtype. Conversely, vaccination of farm workers will reduce the amounts of viruses they shed if infected during human influenza outbreaks, and thereby limit the potential for human influenza virus infection of their pigs.

- **Sick-leave policies** - To further reduce the chances for infection of pigs with human influenza viruses, the farm owner should provide sick-leave policies for employees that encourage them to remain away from work when they are suffering from acute respiratory infections. People typically shed influenza viruses for approximately 3-7 days, with the period of peak shedding correlated with the time of most severe clinical illness.

- **Ventilation** - Ventilation systems in containment production facilities should be designed to minimize re-circulation of air within animal housing rooms. This is important to reduce the exposure of pigs to viruses from other pigs, to reduce their exposure to human influenza viruses, and conversely, to reduce exposure of workers to swine influenza viruses.

- **Basic hygiene practices** - Workers should change clothes prior to leaving swine barns for office facilities, food breaks or their homes. In addition, hand-to-face contact should be minimized and hand-washing stations should be available throughout the animal housing areas. Influenza viruses spread not just by inhalation of aerosolized virus, but also by eye and nose contact with droplets of respiratory secretions.

Interspecies transmission among pigs and birds: The global reservoir of influenza viruses in waterfowl, the examples of infection of pigs with waterfowl-origin influenza viruses, the risks for reassortment of avian viruses with swine and/or human influenza viruses in pigs, and the risk for transmission of influenza viruses from pigs to domestic turkeys all indicate that contact between pigs and both wild and domestic fowl should be minimized. The following factors are potentially useful to reduce transmission of influenza viruses between birds and pigs:

- **Bird-proofing** - All doorways, windows and air-flow vents in swine housing units should be adequately sealed or screened to prevent entrance of birds. Although small birds such as sparrows, swallows, finches, wrens etc. are not thought to be important in the overall ecology of influenza viruses, they may carry influenza viruses from waterfowl feces into barns on their bodies.

- **Water treatment** - Do not use untreated surface water (because of waterfowl fecal contamination with influenza viruses) as either drinking water or water for cleaning in swine facilities. Likewise, it may be prudent to attempt to minimize waterfowl use of farm lagoons.

- **Separation of pig and bird production** - Do not raise pigs and domestic fowl on the same premises.

- **Feed security** - Keep pig feed in closed containers to prevent contamination with feces from over-flying waterfowl.

- **Worker biosecurity** - Provide boots for workers that are worn only within the pig housing units, thus eliminating the chance to carry bird feces into housing units from outdoors.

These recommendations clearly cannot apply to production units in which pigs are raised outdoors. Outdoor housing places pigs at increased risk for infection with avian influenza viruses.

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